REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 1-29 are pending in this application, new claims 27-29 having been added. Claims 7, 9, 11, 16, and 19-24 are herein amended.

The amendment to claim 7, introducing a comma between "addition" and "substitution" merely corrects a punctuation error. The amendment to claim 7, replacing "50%" with "90%" is supported in the specification, *e.g.*, at page 15, line 7. The amendment to claim 7, replacing "and/or" with "and", finds support in original claim 7. The amendment to claim 9, inserting "wherein the polypeptide has a cysteine knot" is supported in the specification, *e.g.*, at page 3, line 1-15. The amendment to claim 11 merely deletes "-of said polypeptide variant as recited in any one of claims 1 to 10" from the claim The amendment to claim 16, replacing "Host" with "An isolated host", is made according to the Examiner's suggestion (see section III below) and is supported in the specification, *e.g.*, at page 17, lines 1-6, where it is inferred that the host cells are isolated host cells because the examples provided are isolated host cells. The amendment to claim 19, deleting "claim", merely corrects a typographical duplication error. The amendment to claim 20, replacing "REQ" with "SEQ", merely corrects a typographical error identified by the Examiner. The amendment to claim 21 merely deletes the subject matter "such as preferably E. coli" from the claim. The amendment to claim 22 merely deletes the subject matter "preferably a yeast, plant or insect cell, CHO or COS cell" from the claim. The amendment to claim 23 merely deletes the subject matter "and, optionally, physiologically compatible additives" from the claim. The amendment to claim 24, converting a use claim to a method of use claim, is supported in the specification, *e.g.* at page 13, lines 7-9, page 20, lines 7-8 and 20-25, page 21, lines 3-5 and 10-16, and in original claim 24. In particular, support for administering a polypeptide variant to a human or animal is provided at page 13, lines 7-9. Support for "in need of bone formation or repair" is provided at page 20, lines 7-8 and page 21, lines 14-16. Support for treatment "suffering from a wound" is provided at page 20, lines 23-25 and page 21, lines 12-13. Support for "inflammation" is provided at page 20, lines 20-23.

Support for "cancer" is provided at page 21, lines 3-5 and 10-11. No new matter is added by the amendments to claims 7, 11, 16, and 19-24.

New dependent claims 27-29 are added. New claim 27 is dependent on claim 21 and recites the prokaryotic host cell "*E. coli*". Support for new claim 27 is provided in original claim 21. New claim 28 is dependent on claim 22 and recites in Markush structure the following eukaryotic cells: a yeast cell, a plant cell, an insect cell, CHO cells, and COS cells. Support for new claim 28 is provided in original claim 22. New claim 29 is dependent on claim 23 and recites "further comprising at least one physiologically compatible additive". Support for new claim 29 is provided in original claim 23. No new matter is added by the addition of new claims 27-29.

Applicants noticed minor discrepancies between the pending claims and the marked up version of the changes to the claims in the preliminary amendment filed August 13, 2001. Accordingly, Applicants have provided a revised marked up version of the changes to the claims made in the preliminary amendment filed August 13, 2001 in the Appendix following the remarks.

II. Election/Restrictions

The Examiner did not find Applicants' traversal of the restriction requirement in the previous response persuasive and has made the restriction final. In particular, the Examiner states that the common structural elements (K, H, R) are known in the art, heparin-binding sequences are taught by the prior art, increased heparin-binding would result from incorporation of such sequences into a polypeptide, and heparin-binding sequences within the scope of the generic claims are also known in the art. Applicants respectfully request that the Examiner reconsider the restriction requirement in light of the following.

The Examiner's position is based on an apparent misunderstanding of the nature of the common structural feature between SEQ ID NOS:1 and 2. It is not the particular amino acids, but the arrangement of the basic and non-basic amino acids in the hexapeptides as

identified in SEQ ID NOS:1 and 2 that constitute the common structural feature. The hexapeptides provide a uniform structural motif, namely, the combination of X_1-X_3 and X_4-X_6. SEQ ID NO:1 and SEQ ID NO:2 have the following technical features in common: (a) the first three positions, X_1-X_3,comprise at least two positively charged (basic) amino acid residues being capable of interacting with the negatively charged sulfated glucosaminoglucanes; and (b) the subsequent three positions, X_4-X_6, are all non-basic amino acids. For X_1-X_3, the options are BBB or BB- (SEQ ID NO:1) and BNB (SEQ ID NO:2), where "B" is a basic amino acid, "N" is a non-basic amino acid, and "-" is no amino acid. This common structural motif establishes the structural unity of SEQ ID NOS:1 and 2.

Contrary to the Examiner's contention, this common structural feature, comprising heparin-binding sequences within the scope of generic claim 1, was not known in the art. As discussed in detail below (sections V and VI), the cited references do not disclose the heparin-binding sequences of the polypeptide variants of claim 1. For the reasons stated in the previous response, there is also a common functional feature, not known in the art, linking together SEQ ID NOS:1 and 2. The Examiner has not challenged this common functional feature. Thus, SEQ ID NOS:1 and 2 share both common structural and functional features conferring distinction over the cited art. In view of the special technical feature shared by these sequences, Applicants respectfully submit that restriction between them should not be required.

III. Claim Objections

Claims 1, 2, 4-9, and 11-26 are objected to because they encompass non-elected inventions. If the Examiner finds that the above argument is not persuasive and maintains the restriction requirement, and such requirement is upheld on petition should Applicants elect to file a petition, then Applicants will delete SEQ ID NO:2 from claims 1, 17, and 20.

The Examiner noted that there is a typographical error in claim 20. Applicants have amended claim 20 accordingly, replacing "REQ" with "SEQ".

IV. Claim Rejections under 35 U.S.C. § 101

Claim 16 is rejected under 35 U.S.C. § 101 because the Examiner alleges that the claimed invention is directed to non-statutory subject matter. In particular, the Examiner contends that "Host cell" recited in claim 16 encompasses the host cell as is occurs in nature, and suggests amending claim 16 to recite "An isolated host cell". Applicants have amended claim 16 according to the Examiner's suggestion, thereby rendering moot the rejection of claim 16.

Claim 24 is rejected under 35 U.S.C. § 101 because the claim 24 recites a use without setting forth any steps, resulting in an improper process claim. Applicants have amended claim 24 accordingly, thereby rendering moot the rejection of claim 24.

V. Claim Rejections under 35 U.S.C. § 102

Claims 1, 2, 4-9, and 11-26 are rejected under 35 U.S.C. § 102(e) as being anticipated by US patent application 2001/0020086 A1 ("086 application"). The Examiner cites the '086 application, as discussing a heparin-binding domain with the amino acid sequence CKRKCN, supposedly taken from Hata et al. (1993). J. Biol. Chem. 268:8447-8457, as well as growth factors using such heparin-binding domains. The Examiner alleges that CKRKCN comprises SEQ ID NO:1. Applicants respectfully traverse this rejection.

The heparin-binding domain cited in the '086 application does not anticipate the polypeptide variants of claim 1. The Examiner has erroneously described the heparin-binding domain cited in the '086 application as CKRKCN. Instead, the sequence in Table 1 of the '086 application is CRKRCN, accompanied by a citation to the Hata et al. reference. Further, the sequence in the Hata et al. reference is CRKNRC. It is unclear as to which of these sequences the Examiner is referring to that allegedly anticipates the polypeptide variants of claim 1. However, none of them meets the requirements of SEQ ID NO:1 or SEQ ID NO:2, in which X_1 must be a basic amino acid (R, K, or H) and X_4-X_6 cannot be basic amino acids. For sequences CKRKCN, CRKRCN, and CRKNRC, X_1 is a non-basic amino acid, and either X_4 or X_5 is a basic amino acid. The following Table 1 illustrates that none of these three sequences meet the structural requirements of claim 1.

Table 1

	X_1	X_2	X_3	X_4	X_5	X_6
SEQ ID NO:1	K, R, H	K, R, H	K, R, H, or no AA	not K, R, H	not K, R, H or no AA	not K, R, H or no AA
SEQ ID NO:2	K, R, H	not K, R, H	K, R, H	not K, R, H	not K, R, H or no AA	not K, R, H or no AA
Cited by Examiner	C	**K**	**R**	K	**C**	**N**
'086 application.	C	**R**	**K**	R	**C**	**N**
Hata et al. reference	C	**R**	**K**	**N**	R	**C**

Table 1 demonstrates that the sequences cited by the Examiner, the '086 application, and the Hata et al. reference, do not meet the conditions of claim 1, in particular the conditions for X_1 and X_4 or X_5. Consequently, the '086 application does not anticipate the polypeptide variants of claim 1. The remaining claims depend on claim 1, directly or indirectly, and are distinguished for the same reasons. As such, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 2, 4-9, and 11-26 under 35 U.S.C. § 102(e).

VI. Claim Rejections under 35 U.S.C. § 103

Claims 1, 2, 4-7, 9, and 11-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the '086 application in view of US patent 5,652,332 ("332 patent"). The Examiner cites the '086 application, as discussing a particular heparin-binding domain and growth factors using heparin-binding domains as set forth above, but teaching no other peptides within the scope of the instant claims. The Examiner cites the '332 patent, as discussing heparin-binding sequences of the human bacteriocidal/permeability-increasing protein (BPI), BPI.2 and BPI.3, that comprises SEQ ID NO:1. The Examiner alleges that "it would be obvious to the artisan of ordinary skill to combine the teachings of the '086 application and the '332 patent to use BPI.2 or BPI.3 to form heparin-binding variants. The Examiner alleges that one of ordinary skill would be motivated to do so because the '086 application teaches uses for such variants, and

the '332 patent teaches alternative peptides that would be expected to also function for the same purposes." Applicants respectfully traverse this rejection.

The combination of prior art references, the '086 application and the '332 patent, does not teach or suggest all the claim limitations of claim 1. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As demonstrated above, the heparin-binding domain cited in the '086 application does not meet the structural requirements of claim 1. As demonstrated in Table 2, the heparin-binding domains cited by the Examiner in the '332 patent, BPI.2 and BPI.3, also do not meet the structural requirements of claim 1.

Table 2

	X_1	X_2	X_3	X_4	X_5	X_6
SEQ ID NO:1	K, R, H	K, R, H	K, R, H, or no AA	not K, R, H	not K, R, H or no AA	not K, R, H or no AA
SEQ ID NO:2	K, R, H	not K, R, H	K, R, H	not K, R, H	not K, R, H or no AA	not K, R, H or no AA
'086 application	C	**R**	**K**	R	**C**	**N**
BPI.2 in '332 patent	**K**	**R**	**no AA**	**F**	**L**	K
BPI.3 in '332 patent	**K**	**R**	**no AA**	**F**	**L**	K

Table 2 demonstrates that BPI.2 and BPI.3 do not meet the conditions of claim 1, in particular the condition for X_6. BPI.2 has the sequence IKISGKWKAQKRFLK and BPI.3 has the sequence NVGLKFSISNANIKISGKWKAQKRFLK. By visual inspection the common sequence KRFLK has the closest alignment with the hexapeptide structure of claim 1: BB-NNB, where "B" is a basic amino acid, "N" is a non-basic amino acid, and "-" is no amino acid B. However, neither BPI.2 nor BPI.3 corresponds to the hexapeptide of claim 1 because X_6 of SEQ ID NOS: 1 and 2 is a non-basic amino acid, whereas the corresponding position in BPI.2 and

BPI.3 is a basic amino acid. Therefore, the '332 patent does not teach or suggest the heparin-binding domains of claim 1. The '332 patent does not compensate for the deficiencies in the '086 application, which also does not teach or suggest the heparin-binding domains of claim 1. Because the heparin-binding domains disclosed in the '086 application and the '332 patent do not satisfy the conditions of claim 1, and the cited references do not compensate for the other's deficiencies, the combination of the prior art references do not teach or suggest all the claim limitations of the polypeptide variants of claim 1. Thus, the Examiner has failed to establish a *prima facie* case of obviousness against claim 1, and Applicants respectfully request that the rejection of claims 1, 2, 4-7, 9, and 11-26 under 35 U.S.C. § 103(a) be withdrawn.

Claim 8 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the '086 application in view of Linkhart et al. ("Linkhart"). The Examiner cites Linkhart as discussing BMPs as being related to TGF-β, osteoinductive and useful for bone healing, and the need for matrices to use BMPs. The Examiner alleges that it would be obvious to one of ordinary skill in the art to combine the teachings of the '086 application and Linkhart to modify BMPs with heparin binding sites so that they can be used with matrices like heparin and fibrin. The Examiner alleges that the motivation to combine the references is that the '086 application teaches ways to modify growth factors to be attached to matrices and Linkhart teaches that it is useful to attach BMPs to matrices. Applicants respectfully traverse this rejection.

Claim 8 depends from claim 1 and is non-obvious for at least the same reasons as discussed above for claims 1, 2, 4-7, 9, and 11-26.

VII. Claim Rejections under 35 U.S.C. § 112

A. 35 U.S.C. § 112, first paragraph

1. Enablement

Claims 1, 2, 4-9, and 11-26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for all peptides

meeting the limitations of SEQ ID NO:1. The Examiner alleges that "the claims are very broad, encompassing sequences that need not have a single residue in common" and that "there is no guidance in the specification to indicate that these peptides are correctly described by Applicant's generic sequence, so that the artisan could predictably use other members of the genus to increase heparin binding of polypeptides." The Examiner alleges that neither the prior art nor the instant specification provides sufficient guidance to indicate members of the claims genus could predictably be used to bind heparin. The Examiner alleges that due to the complexity and unpredictability of the nature of the invention and art in terms of the diversity of peptides that bind heparin, and the lack of direction of guidance for using peptides that are not identical to those already shown to function, it would require undue experimentation to use the invention commensurate with the scope of the claims. Applicants respectfully traverse this rejection.

As an initial matter, there appear to be several misunderstandings in the instant Office Action. The Examiner mistakenly alleges that five positions of the hexapeptide sequence of claim 1 are required, and that three of these can be any of twenty-three possibilities. In fact, for SEQ ID NOS: 1 and 2, only three or four positions, respectively, are required, and there are seventeen non-basic amino acid possibilities. The Examiner is also mistaken in stating that the art teaches three sequences that meet the structural limitations of the heparin-binding domains of claim 1. As demonstrated in sections V and VI above, none of the heparin-binding sequences cited by the Examiner meet the structural limitations of the oligopeptides of claim 1. Finally, contrary to the Examiner's contention that claim 1 encompasses all proteins, claim 1 is directed to polypeptides selected from among members of the DVR family including the TGF-β superfamily.

The Examiner has alleged that the specification provides insufficient direction or guidance regarding how to predictably use heparin-binding domains as broadly defined by the claims. However, other than comments regarding "the loosely defined features of Applicant's SEQ ID NO:1" (which has been addressed in detail in section II above), the Examiner has not explained why the skilled artisan could not identify a member of the genus or predictably use other members of the genus, and has not set forth any objective evidence or reasoning to doubt

that a sequence that satisfies the requirements of SEQ ID NO: 1 or 2 confers heparin-binding ability to a polypeptide of claim 1. As stated in the MPEP § 2164.05, page 2100-191, "the Examiner should **never** make the determination based on personal opinion". Contrary to the Examiner's mere allegation, the disclosure provides sufficient guidance so that one of ordinary skill could predictably use other members of the genus to increase the heparin binding ability of heterologous polypeptides.

In fact, one would expect other members having the claimed motifs to share the heparin-binding of the exemplified species (T3 and T4) because the heparin-binding results from the combination of the charge distribution of the heparin-type substances and the exemplified species. The negatively charged groups of heparin-type substances are arranged in triplets and match up with the positively charged groups (basic amino acids), which are also arranged in triplets, of the exemplified species. The claimed motifs require that its members have the same charge distribution and triplet arrangement as the exemplified species. One would therefore expect them to bind heparin, as do the exemplified sequences.

The introduction of a heparin binding motif into a member of the DVR family does not introduce significant additional unpredictability. The type of polypeptide into which the claimed motifs is incorporated would be expected to be largely irrelevant to the heparin-binding of the claimed motifs. A wide variety of types of proteins have heparin-binding domains, including growth factors, BPI, proteases, adhesion molecules, fibronectin, and lipoprotein lipase (see the '086 application and '332 patent), showing that capacity of a heparin binding domain to bind heparin is not critically dependent on the nature of flanking sequences. For these reasons, one would expect at least a reasonable number of the polypeptide variants recited in the claims to have heparin binding activity.

The test under *In reWands,* 8 USPQ2d 1400 (Fed. Cir. 1988), is not whether each and every possible variant within the present claims has heparin binding activity but rather whether it is feasible to screen a reasonable number that do without undue experimentation. The issue in *Wands* was whether the specification of the *Wands* patent enabled production of a class

of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using Kohler Milstein technology. As the Examiner is no doubt aware, Kohler Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. The evidence indicated that only a small percentage of the hybridomas to be screened would produce antibodies having the desired property. Nevertheless, the court found that "practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*" (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled.

Here, as in *Wands* a reasonable number of variants can be screened for heparin binding activity by repetition of routine steps. There is nothing difficult in making polypeptide variants falling in the scope of claim 1. The specification defines the structure of the heparin-binding domains, which comprise a specific combination of amino acids: X_1-X_3 , in which 2 out of 3 are basic amino acids; followed by X_4-X_6, in which none is a non-basic amino acid. With this definition, one would known whether any oligopeptide falls within the scope of the claim 1. The polypeptides of claim 1, members of the DVR family, are well-known in the art. Mere standard molecular biology techniques are required to make the polypeptide variants of claim 1. There is also nothing difficult in testing the polypeptide variants of claim 1 for their ability to bind heparin. The disclosure provides simple heparin-binding assays, which are well-known in the art. Thus, a reasonable number of variants having heparin activity would be obtained by routine molecular biology and a simple *in vitro* assay. As held by *Wands,* practitioners of the art are prepared to undertake this type of screening to identify molecules having a desired property. For these reasons, Applicants respectfully request that the rejection of claims 1, 2, 4-9, and 11-26, for lack of enablement, be withdrawn.

The Examiner alleges that claim 7 lacks enablement for proteins with alterations, additions, substitutions, insertions, inversions, and/or deletions, with no limitation as to structure and no functional limitation other than that the encompassed proteins maintain the "biological activity" of the original molecule. The Examiner alleges that claim 7 encompasses a potentially

infinite number of variations to undefined proteins, with no particular activity required. The Examiner alleges that the specification provides no guidance as to how such a large number of unrelated proteins could be made and used. Thus, without further guidance, it would require undue experimentation for the artisan to make and use such proteins as broadly claimed. Applicants respectfully traverse this rejection insofar as it might be applied to amended claim 7.

Claim 7 has been amended to require both structural and functional limitations. The additions, substitutions and the like specified in claim 7 occur not within the recited heparin binding motif but in the polypeptide into which such motif is introduced. Claim 1 specifies that this polypeptide is a member of the DVR family. Therefore, the recited additions, substitutions and the like represent variants of the DVR family. These variants are constrained in the amended claims by specifying that the altered polypeptide has at least 90% homology to the unaltered polypeptide and at least some (10%) of its biological activity. Claims of this type specifying variants of a polypeptide constrained by 90% homology and retention of functional activity have been routinely granted by the PTO. Therefore, the recitation of variation in the polypeptide into which a heparin binding motif is introduced in claim 7 should not result in additional issues of enablement beyond those already addressed with respect to claim 1.

The Examiner alleges that claim 9 lacks enablement for placement of the heparin-binding residue before "the" cysteine knot, since not all proteins have "a" cysteine knot. Applicants respectfully traverse this rejection insofar as it might be applied to amended claim 9.

Applicants have amended claim 9 to recite that the oligopeptides of claim 1 are inserted before the cysteine knot in only those polypeptides of claim 1 that have a cysteine knot. As such, Applicants respectfully request that the rejection of claim 9, for lack of enablement, be withdrawn.

The Examiner alleges that claims 24-26 lack enablement commensurate in scope with the claims since the artisan could not predictably use all the variants within the scope of the

claims for wound healing or other treatments; claim 1 encompasses modifications to all proteins. Applicants respectfully traverse this rejection.

The therapeutic activity of the polypeptide variants of claim 1 results from improved heparin binding ability. Therefore, the issue of whether the skilled artisan could predictably use all the variants within the scope of the claims is essentially the same as the enablement issue raised by Examiner for claim 1, as discussed above. For the same reasons as above, Applicants respectfully request that the rejection of claims 24-26, for lack of enablement, be withdrawn.

2. Written Description

Claims 1, 2, 4-9, and 11-25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus." The Examiner alleges that "since there are no required common regions, no characteristic physical, structural or functional features are imparted to the invention. The skilled artisan thus cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the method of isolation. There is no guidance in the specification or in the prior art to indicate that the very limited common features of the claimed genus are sufficient to impart the characteristics function, thus the subject matter is not sufficiently described so as to indicate to the artisan that Applicant is in possession of a genus of heparin-binding peptides". Applicants respectfully traverse this rejection.

For originally filed claims, as here, the issue of adequate written description is addressed by MPEP § 2163 at p. 2100-156, second column et seq., which states that despite a "strong presumption that an adequate written description of the claim invention is present when the application is filed," "the issue of written description may arise even for an original claim" if the "claimed invention as a whole require[s] an essential or critical feature which is not

adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." Written description can be provided by description of structural features commonly possessed by members of the genus that distinguishes them from others. *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The issue of written description for original claims directed to polypeptide variants is addressed in Example 13 of the USPTO's Revised Interim Written Description Guidelines Training Materials. A genus claim to an isolated variant, which means a protein having one or more amino acid substitutions, deletions, insertions and/or additions, of the protein of claim 1 is rejected when: the specification and claim do not indicate what distinguishing attributes are shared by the members of the genus and do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made, and the specification does not provide any description of variants. An applicant is not in possession of the claimed genus where the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and the genus is highly variant.

Here, the specification and claims do describe structural features commonly possessed by members of the genus that distinguishes them from others, as required by *Lilly*. The specification and claims also satisfy the criteria of Example 13 of the Revised Interim Guidelines. The specification and claim 1 defines the distinguishing structural feature as a polypeptide into which has been introduced an oligopeptide of a recited formula. The oligopeptides of claim 1 provide a common structural motif, namely, the combination of X_1-X_3 and X_4-X_6, wherein X_1-X_3comprise at least two positively charged (basic) amino acid residues being capable of interacting with the negatively charged sulfated glucosaminoglucanes, and X_4-X_6 are all non-basic amino acids. As has been discussed above, such polypeptide variants were not previously known in the art. The structural distinctions in the claimed therefore distinguish the claimed polypeptide variants from others. The recited formula also constrains the extent of variation from the working examples of two polypeptide variants disclosed in the specification. For the reasons discussed above, one would expect that other variants within the formula would have similar activity. Finally, the genus is not highly variant, because the oligopeptides

sequences have specific structural features, as discussed above, and the polypeptides of claim 1 are not all proteins as alleged by the Examiner, but are limited to the members of the DVR family including the TGF-β superfamily. For these reasons, Applicants respectfully submit that the present claims fulfill the requirements of *Lilly* and the Revised Interim Guidelines.

For this reason, and because the Examiner has not shown that an essential or critical feature of the claimed invention has been omitted, it respectfully submitted that the Examiner has failed to overcome the strong presumption of an adequate written description of original claims. Therefore, Applicants respectfully request that the rejection of claims 1, 2, 4-9, and 11-25, for lack of written description, be withdrawn.

B. 35 U.S.C. § 112, second paragraph

Claims 21-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For claims 21-23, the Examiner contends that the phrases "such as" and "preferably" render the claims indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. For claim 24, the Examiner states that "since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass."

Applicants have amended claims 21-23 by canceling the terms and limitations following them that allegedly render these claims indefinite, thereby mooting the rejection of claims 21-23. Applicants have added new claims wherein the limitations are provided in dependent claims. No new matter is added by these new claims.

Applicants have amended claim 24 to recite the step of administering the polypeptide variant of claim 1 to a human or animal. This amendment to claim 24 is supported by the specification. By reciting a step, the rejection of claim 24 is mooted.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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APPENDIX

REVISED MARKED-UP VERSION OF THE CHANGES TO THE CLAIMS (FROM PRELIMINARY AMENDMENT FILED AUGUST 13, 2001)

3. (amended) A polypeptide variant as recited in [claim 1 or 2] claim 1, characterized in said oligopeptide comprises amino acid sequence RKRA (SEQ ID NO:3) or RKRAKHKQ (SEQ ID NO:4).

4. (amended) A polypeptide variant as recited in [any one of claims 1 to 3] claim 1, characterized in said oligopeptide is added to the N-terminus and/or inserted into the N-terminal region, and/or substitutes a part of the N-terminal region.

5. (amended) A polypeptide variant as recited in [any one of claims 1 to 4] claim 1, characterized in that the amino acid sequence of said polypeptide variant further contains a sequence of relevance to recombinant expression at the N-terminus, said sequence of relevance to recombinant expression being M or MZ, where M stands for methionine and Z stands for one or more amino acids.

6. (amended) A polypeptide variant as recited in [any one of claims 1 to 5] claim 1, characterized in that said polypeptide variant further contains a His-tag.

7. (amended) A polypeptide variant as recited in [any one of claims 1 to 6] claim 1, characterized in that said polypeptide is altered by addition, substitution, insertion, inversion, and/or deletion, where said polypeptide altered by addition substitution, insertion, inversion and/or deletion shows at least 10% of the biological activity of the unaltered polypeptide, and/or at least 50% homology to the unaltered polypeptide.

8. (amended) A polypeptide variant as recited in [any one of claims 1 to 7] claim 1, characterized in that said polypeptide is BMP-2, BMP-4, BMP-5, BMP-6, BMP-7/OP-l, or BMP-8/OP-2.

9. (amended) A polypeptide variant as recited in [any one of claims 1 to 8] claim 1, characterized in that said oligopeptide is inserted before the cysteine knot.

10. (amended) A polypeptide variant as recited in [claim 8 or 9] claim 8, characterized in that said polypeptide variant has the amino acid sequence SEQ ID NO:5 (T3) or SEQ ID NO:6 (T4).

11. (amended) A polypeptide variant as recited in [any one of claims 1 to 10] claim 1, characterized in that said polypeptide variant is a polymer, oligomer, or dimer of said polypeptide variant as recited in ***any one of claims 1 to 10***.

12. (amended) A nucleic acid molecule, comprising a nucleic acid sequence encoding a polypeptide variant as recited in [any one of claims 1 to 11] claim 1.

14. (amended) A nucleic acid molecule as recited in claim [12 or 13] claim 12, further comprising a promoter suited to control expression, wherein said nucleic acid sequence encoding a polypeptide variant is under the control of said promoter.

15. (amended) A nucleic acid molecule as recited in [any one of claims 12 to 14] claim 12, wherein said nucleic acid molecule contains at least part of a vector.

16. (amended) Host cell, containing a nucleic acid molecule as recited in [any one of claims 12 to 15] claim 12, wherein said host cell is a prokaryotic or eukaryotic cell suitable for expression of said nucleic acid molecule.

17. (amended) A process for producing a polypeptide variant with increased heparin-binding ability as recited in [any one of claims 1 to 11] claim 1, comprising:

addition to the amino acid sequence of a polypeptide of at least one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2; and/or

insertion into the amino acid sequence of a polypeptide of at least one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2; and/or

substitution of at least one oligopeptide sequence naturally occurring within the amino acid sequence of a polypeptide by one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2.

19. (amended) A process as recited in claim [17 or 18] claim 17, characterized in that said process comprises gene technological processes.

20. (amended) A process as recited in [any one of claims 17 to 19] claim 17, characterized in that said process comprises:

a) in vitro mutagenesis of a nucleic acid encoding a polypeptide, so that

(i) to the nucleic acid encoding said polypeptide is added at least one nucleic acid encoding an oligopeptide containing an amino acid sequence that is selected from SEQ ID NO:1 or SEQ ID NO:2; and/or

(ii) into the nucleic acid encoding said polypeptide is inserted at least one nucleic acid encoding an oligopeptide containing an amino acid sequence that is selected from SEQ ID NO:1 or REQ ID NO:2; and/or

(iii) at least one nucleic acid sequence naturally occurring within the nucleic acid sequence encoding said polypeptide is substituted by a nucleic acid sequence encoding an oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2;

b) cloning of the mutated nucleic acid into a suitable expression vector;

c) transformation/transfection of a suitable host cell with the expression vector obtained;

d) cultivation of said transformed/transfected host cell under conditions suitable for expression;

e) isolation, and if necessary renaturation, of the expressed polypeptide variant.

21. (amended) A process as recited in [any one of claims 17 to 20] claim 17, characterized in that said process is carried out within a prokaryotic host cell such as preferably E. coli.

22. (amended) A process as recited in [any one of claims 17 to 20] claim 17, characterized in that said process is carried out within a eukaryotic cell, preferably a yeast, plant or insect cell, CHO or COS cell.

23. (amended) A pharmaceutical composition, comprising a polypeptide variant as recited in [any one of claims 1 to 11] claim 1 and, optionally, physiologically compatible additives.

24. (amended) Use of a polypeptide variant as recited in [any one of claims 1 to 11] claim 1 to stimulate osteogenesis or wound healing, or to treat inflammation or cancer.

25. (amended) A composition for osteoinduction, comprising a polypeptide variant as recited in [any one of claims 1 to 11] claim 1 and a carrier selected from among heparin, hydroxyapatite, hyaluronic acid, synthetic polymers, and collagen.

26. (amended) An osteoinductive matrix, characterized in that said matrix contains or is coated with heparin or heparin-like substances and polypeptide variants as recited in [any one of claims 1 to 11] claim 1 are adsorbed to said heparin or heparin-like substances.